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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/980,913	05/21/2002	Ernest Arenas	0380-P02709USO	3833

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EXAMINER	
MCGILLEM, LAURA L	
ART UNIT	**PAPER NUMBER**
1636	

DATE MAILED: 09/13/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Advisory Action Before the Filing of an Appeal Brief	Application No. 09/980,913	Applicant(s) ARENAS ET AL.	
	Examiner Laura McGillem	Art Unit 1636	

--The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

THE REPLY FILED 24 August 2006 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE.

1. ☒ The reply was filed after a final rejection, but prior to or on the same day as filing a Notice of Appeal. To avoid abandonment of this application, applicant must timely file one of the following replies: (1) an amendment, affidavit, or other evidence, which places the application in condition for allowance; (2) a Notice of Appeal (with appeal fee) in compliance with 37 CFR 41.31; or (3) a Request for Continued Examination (RCE) in compliance with 37 CFR 1.114. The reply must be filed within one of the following time periods:
   a) ☒ The period for reply expires 4 months from the mailing date of the final rejection.
   b) ☐ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection.

   Examiner Note: If box 1 is checked, check either box (a) or (b). ONLY CHECK BOX (b) WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

NOTICE OF APPEAL

2. ☐ The Notice of Appeal was filed on _____. A brief in compliance with 37 CFR 41.37 must be filed within two months of the date of filing the Notice of Appeal (37 CFR 41.37(a)), or any extension thereof (37 CFR 41.37(e)), to avoid dismissal of the appeal. Since a Notice of Appeal has been filed, any reply must be filed within the time period set forth in 37 CFR 41.37(a).

AMENDMENTS

3. ☐ The proposed amendment(s) filed after a final rejection, but prior to the date of filing a brief, will not be entered because
   (a) ☐ They raise new issues that would require further consideration and/or search (see NOTE below);
   (b) ☐ They raise the issue of new matter (see NOTE below);
   (c) ☐ They are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or
   (d) ☐ They present additional claims without canceling a corresponding number of finally rejected claims.

   NOTE: _____. (See 37 CFR 1.116 and 41.33(a)).
4. ☐ The amendments are not in compliance with 37 CFR 1.121. See attached Notice of Non-Compliant Amendment (PTOL-324).
5. ☐ Applicant's reply has overcome the following rejection(s): _____.
6. ☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).
7. ☒ For purposes of appeal, the proposed amendment(s): a) ☐ will not be entered, or b) ☒ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.
   The status of the claim(s) is (or will be) as follows:
   Claim(s) allowed: _____.
   Claim(s) objected to: _____.
   Claim(s) rejected: *1-3 and 5-12*.
   Claim(s) withdrawn from consideration: _____.

AFFIDAVIT OR OTHER EVIDENCE

8. ☐ The affidavit or other evidence filed after a final action, but before or on the date of filing a Notice of Appeal will not be entered because applicant failed to provide a showing of good and sufficient reasons why the affidavit or other evidence is necessary and was not earlier presented. See 37 CFR 1.116(e).
9. ☐ The affidavit or other evidence filed after the date of filing a Notice of Appeal, but prior to the date of filing a brief, will not be entered because the affidavit or other evidence failed to overcome all rejections under appeal and/or appellant fails to provide a showing a good and sufficient reasons why it is necessary and was not earlier presented. See 37 CFR 41.33(d)(1).
10. ☐ The affidavit or other evidence is entered. An explanation of the status of the claims after entry is below or attached.

REQUEST FOR RECONSIDERATION/OTHER

11. ☒ The request for reconsideration has been considered but does NOT place the application in condition for allowance because: See Continuation Sheet.
12. ☐ Note the attached Information Disclosure Statement(s). (PTO/SB/08) Paper No(s). _____
13. ☐ Other: _____.

Continuation of 11. does NOT place the application in condition for allowance because: Applicants submit that the present case has notable similarities to Ex parte Levengood, 28 USPQ 1300 (BPAI 1993). The claims were rejected as allegedly obvious based on the combined disclosures of three references, Levengood, Janick and Holl. Applicants submit that like the Bowen et al reference in this case, the Levengood prior art reference was concerned with increasing the proportion of mutants in a single plant species by applying electrical field gradients to the plant. Applicants submit that the Levengood prior art reference omitted certain elements of patentable significance called for in the claimed method, as does the Bowen et al reference in this case. The secondary references, Janick and Holl, were not concerned with the basic methodology of the claimed invention, involving application of electrical current, but merely disclosed standard grafting and/or genetic engineering procedures. Applicants submit that this is like Takeshima et al, which discloses only the known survival-promoting effect of astrocyte factors on neural cells already having the dopaminergic phenotype.

Applicants submit that the instant case, as in Levengood, the references cited as evidence of obviousness "fall far short of providing the 'motivation' or suggestion' to assemble their teachings into a viable process". Applicants submit that the examiner appears to have ignored the well-established principle that it is improper within the framework of §103 to pick and choose from any one reference only so much of it as will support a given position, to the exclusion of other parts necessary to the full appreciation of what such reference fairly teaches to one of ordinary skill in the art as in In re Wesslau, 147 USPQ 391 (CCPA 1965). Applicants submit that the combined disclosures of Bowen et al and Takeshima et al fail to teach or suggest the co-culturing of neural stem cells or neural progenitor cells, expressing Nurr1 above basal levels, with Type 1 astrocytes of the ventral mesencephalon for any purpose, much less for inducing in the neural stem cells or progenitor cells a dopaminergic neuronal phenotype.

Applicants submit that in the July 29, 2005 Official Action, the examiner conceded, at page 22, that:

> Bowen et al do not disclose that neuronal stem cells are co-cultured with Type 1 astrocytes of the ventral mesencephalon in order to induce the development of dopaminergic neurons.

Applicants submit that there is no dispute that there are patentable distinctions between applicants' claimed method of inducing a dopaminergic neuronal fate in a neural stem cell or neural progenitor cell and the method for generating dopaminergic cells derived from neural precursors described in Bowen et al. Applicants submit that, in view of the admitted deficiencies in the disclosure of Bowen et al., it was incumbent upon the examiner, in order to meet the burden of proof under § 103, to cite additional prior art that not only discloses the elements that are conceded to be missing from Bowen et al, but also provides a teaching or suggestion that would motivate one of ordinary skill in the art to modify the method of Bowen et al. to include such missing elements and thus arrive at the claimed invention. Applicants submit that Takeshima et al fails to provide the elements missing from the disclosure of Bowen et al, of co-culturing a neural stem cell or neural progenitor cell with a Type I astrocyte of the ventral mesencephalon so as to contact the neural stem cell or neural progenitor cell with one or more astrocyte factors, and thereby induce a dopaminergic neuronal fate in the neural stem cell or neural progenitor cell.

Applicant's arguments filed 8/24/2006 have been fully considered but they are not persuasive. The claims under review in Ex parte Levengood were directed to a method for increasing the proportion of mutants in a subsequent generation of a member of a plant species having a recognized and established phenotype. The method involved contacting a member of a first plant species with whole cells and associated materials of a second species, and simultaneously subjecting the contacted combination to electrophoretic conditions. The Levengood prior art reference taught a method of increasing the proportion of mutants in a single plant species by applying electrical field gradients to the plant, but did not teach that members of a first plant species should be placed in contact with whole cells and associated materials of a second species while simultaneously applying the electrophoretic current. The secondary references of Janick and Holl were used to introduce the step of contacting a first plant species with whole cells and associated materials of a second species.

Although the Levengood case may seem applicable because it concerns similar subject matter, such as culturing cell types together combined with other factors in order to facilitate a change in cells, the actual issues in the Levengood case are different from the instant case. First, the Janick and Holl secondary references are basic horticultural texts that disclose standard grafting and/or genetic engineering procedures. In contrast, the secondary reference of Takeshima et al is a journal article that is focused on the role of astrocytes in the development and survival of embryonic neurons and is directly related to the method of Bowen et al.

Secondly, the ruling in Levengood is based on a "wrong standard of obviousness" stemming from a lack of motivation to combine the Levengood reference with the Janick and Holl references to obviate the claimed methods because the examiner did not provide objective teaching in the prior art or knowledge generally available to the skilled artisan that would lead to combination of the relevant teachings in the references. Instead, the rejection appeared to be based on a suggestion from the disclosure and the assumption that the skilled artisan would be able to combine several well-known techniques because they were known in the art.

The motivation in the instant case is more definitive than that provided in the Levengood case. In the instant case, the combination of the teaching of Bowen et al and Takeshima et al is based on the related disclosure of each and not on the instant specification. Bowen et al discloses increased survival of dopaminergic neurons when in co-culture with astrocytes and Takeshima et al uses a culture of mesencephalic Type 1 astrocytes to support the growth of developing dopaminergic neurons derived from embryonic rat brains. The motivation to combine is the expected benefit of being able to produce a viable culture of dopaminergic neurons, suggested by Bowen et al and actually exemplified by Takeshima. Both the Bowen et al and Takeshima et al references are focused on similar goals, to develop and support the growth of neurons in culture from precursor cells. Applicants submit that the Levengood prior art reference did not suggest that member of a first plant species should be contacted with whole cells and associated materials of a second species while applying electrophoretic current. However, unlike Levengood, Bowen et al does disclose that co-culturing dopaminergic neurons with striatal astrocytes or with conditioned medium from striatal astrocytes has been shown to increase survival of the neurons (see column 3, lines 11-25), which suggests that Bowen et al contemplates co-culture of astrocytes with neurons.

Further, Applicants cite Rockwell International Corp. v. United States, 47 USPQ 2d 1027 (Fed. Cir. 1998) to argue combinations of references. In that case, the Federal Circuit, faced with similarly deficient prior art references, reversed a holding of obviousness stating that "... with respect to obviousness, the trial court could not simply find that these four patents, when combined with each other.., taught the very limitation that admittedly none of them taught separately." Rockwell is a case regarding claims to a process for growing semiconductor films rejected for obviousness using four prior art patents. In Rockwell it was found that not one of the four prior art

patents taught a specific aspect of the process. This is not applicable here since each aspect of the claimed method is taught or contemplated by the cited references.

The basis for all obviousness rejections, in part, is that a patent may not be obtained ... if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. It is not necessary for Bowen et al or Takeshima et al to teach the entire claimed method, because it is the combination of the two that renders the instant method obvious.

Applicants submit that Takeshima et al do not teach exposure of stem or progenitor cells exposed to fate inducing effects of astrocyte factor, a fact which is clearly of patentable significance, considering that the material on which a method is carried out must be accorded weight in determining the non-obviousness of the method according to Ex parte Leonard, 187 USPQ 122 (Bd. Apps. 1974). Ex parte Leonard is a case that involved an underwater adhesive composition, unexpected results obtained from combination of materials and whether it was obvious to combine the materials suitable for lamination under water. Ex parte Leonard is not completely applicable in the instant case because the material in question in the instant case is neural stem or progenitor cells, and since progenitor cells of the central nervous system are taught by Bowen et al it would be obvious to use them in a method combining the teachings of Takeshima et al and Bowen et al. Absent evidence to the contrary, the precursor cell population of the central nervous system as taught by Bowen et al would include neural stem or progenitor cells. It is not necessary for Takeshima et al to teach stem or progenitor cells exposed to fate inducing effects of astrocyte factor and is not necessary for Bowen et al to disclose that neuronal stem cells are co-cultured with Type 1 astrocytes of the ventral mesencephalon in order to induce the development of dopaminergic neurons, because it is the combination of these two references that renders the claimed methods obvious to the skilled artisan.

The inventive method would be obvious to one of ordinary skill in the art in part because Bowen et al teaches a method of directing cell fate for precursor cells of the central nervous system by the expression of a gene coding for Nurr1 in order to direct neuronal precursors to a dopaminergic cell fate, and discloses that co-culturing dopaminergic neurons with striatal astrocytes or with conditioned media from striatal astrocytes has been shown to increase the survival of the neurons. Therefore, from the teaching of Bowen et al, the skilled artisan is aware that Nurr1 can direct neuronal precursors to a dopaminergic cell fate and that co-culturing dopaminergic neurons with striatal astrocytes is beneficial to neuronal survival. The instant claims are not directed toward cell survival, but Bowen et al teach methods of directing neuronal precursors to a dopaminergic cell fate.

Takeshima et al teach that embryonic mesencephalic cells were plated on a confluent monolayer of ventral mesencephalic astrocytes and showed an increase in dopaminergic cell number, and also exhibited changes consistent with neuronal cell development. Takeshima suggests that the Type 1 astrocytes may produce a factor that acts selectively on the dopaminergic neural phenotype (see page 819, paragraph 1, for example). While the initial goal of an assay taught by Takeshima et al was to test the ability of astrocyte-conditioned medium to promote the survival of TH+ cell in culture, they observed an inconsistent increase in the percentage of TH+ neurons which suggested that the astrocytes are the source of a putative factor that "promotes the development of TH+ neurons in culture" (see page 816, right column, 1st paragraph). Thus, while the assay in Takeshima et al was designed to test cell survival in the presence of astrocytes conditioned medium, the results suggested a role for astrocytes in the development of neurons. Therefore, Takeshima et al contemplate a role for astrocyte co-culture in the development of neurons. Given the teaching from Bowen et al that Nurr1 can direct neuronal precursors to a dopaminergic cell fate, co-culturing dopaminergic neurons with striatal astrocytes is beneficial to neuronal survival and the teaching of Takeshima et al that contemplates a roles for astrocytes in the development of neurons, one of ordinary skill in the art would be motivated to express Nurr1 in a neural progenitor cell and co-culture the cells with astrocytes in order to get the beneficial effect of factors from the astrocytes to definitively induce a dopaminergic cell fate in cells, since both references suggest the benefit of culture with astrocytes. It is not necessary for Takeshima et al to use neural stem cell or neural progenitor cells in the methods, because Bowen et al use neural stem cell or neural progenitor cells and it is the combination of the two references that obviate the claimed methods. While survival of differentiated cells is distinctly different from induction of stem cells to a phenotype, differentiation of precursor cells to dopaminergic neurons is taught by Bowen et al and therefore can be contemplated by the skilled artisan. The rejection in question is based upon relevant aspects of each reference and does not constitute "picking and choosing" information from any one reference to support a given position to the exclusion of other parts necessary to full appreciation of the teaching.

DANIEL M. SULLIVAN
PATENT EXAMINER